CHROMIUM UPDATE 1984

ENVIRONMENTAL AND NUTRITIONAL EFFECTS OF CHROMIUM

BY

JOHN F. JAWORSKI

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NATIONAL RESEARCH COUNCIL OF CANADA
NRCC ASSOCIATE COMMITTEE ON SCIENTIFIC CRITERIA
FOR ENVIRONMENTAL QUALITY

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John F. Jaworski

SUBCOMMITTEE ON HEAVY METALS AND CERTAIN OTHER ELEMENTS

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SUMMARY

This monograph covers aspects of Cr biogeochemistry, essentiality and toxicology since the publication in 1976 of "Effects of Chromium in the Canadian Environment" (NRCC No. 15017). Basically, the major advances have occurred in six areas:

(i) Environmental speciation:

In 1976, it was noted that CrIII could be converted to the more toxic CrVI during the chlorination of drinking water. More recently, this oxidation step was found to be catalyzed by manganese dioxide, a common constituent of aerated soils and natural waters (see sections 2.1 and 3.1).

(ii) Analytical methodology:

In 1978, it was realized that sample contamination and lack of background correction in atomic absorption analysis resulted in reported levels of Cr in blood and urine that were 10 to 100 times too high. Earlier low-level analyses should be used with caution (see Sections 5.1.1 and 6.0).

(iii) Nutritional requirements:

In most humans (excluding special subgroups listed below) the daily dietary Cr requirement appears to be satisfied by the ingestion of 8-10 μg $Cr.d^{-1}$ as the "glucose tolerance factor" (a CrIII-organic complex) or by 50-200 μg $Cr.d^{-1}$ as simple CrIII salts (see section 5.1.2).

(iv) Subgroups susceptible to Cr deficiency:

There is evidence for an above-average Cr nutritional requirement, especially in pregnant multiparous women (see section 5.1.5.1), and also in those who exercise strenuously (see Table 5), in the elderly (see section 5.1.5.2), and in insulin-dependent diabetics (see section 5.1.5.3).

(v) Cr and carbohydrate/lipid metabolism:

Especially in the elderly, marginal dysfunction of carbohydrate and lipid metabolism responded to Cr supplementation in almost 50% of cases (see section 5.1.5.2 and Table 5). Cr deficiency may play a role in the etiology of some forms of atherosclerosis (see Section 5.1.5.4).

(vi) Occupational lung cancer:

The recognition of a pulmonary cancer risk in occupational (respiratory) CrVI exposure has been extended to the chrome-plating

industry, in addition to the chromate-producing and chrome-pigment industries, where the risk had already been recognized.

RESEARCH RECOMMENDATIONS

The following research needs were identified:

i) evaluation of the toxic impact of CrVI, produced from CrIII by the action of manganese dioxide in water or soil, and by the chlorination of drinking water;

(ii) epidemiologic and laboratory studies to define the carcinogenic risk of workers and members of the nearby community in the chrome-plating, ferrochrome and chrome refractory industries; and

(iii) clinical and laboratory studies to define the role of adequate Cr nutrition in maintaining normal carbohydrate and lipid metabolism and in prevention or attenuation of such diseases as diabetes and atherosclerosis.

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1.0 INTRODUCTION

Chromium (Cr), depending on its chemical state and its concentration, can be either an ultratrace essential element or a toxic and carcinogenic substance. Extensive research in the 1960s and 1970s elucidated many aspects of its environmental and clinical chemistry and effects (some major reviews: NAS 1974; NIOSH 1975; NRCC 1976; Shapcott and Hubert 1979; EPA 1980; Towill et al. 1980; Saner 1980; Industrial Health Foundation 1981; Burrows 1983a). This review highlights developments since 1976 in the areas of:

- environmental chemistry and speciation (especially conversion of CrIII to CrVI in nature)
- improved methods for low-level Cr analysis
- Cr metabolism, essentiality, dietary requirements and effects of deficiency
- Cr toxicity, mutagenicity and carcinogenicity

Included are sections that deal with effects on aquatic organisms, terrestrial plants and mammals.

2.0 Cr AND AQUATIC ORGANISMS

Average natural levels of Cr are low in both freshwater (≈ 1 µg $Cr.L^{-1}$; Bowen 1979) and saltwater (≈ 0.3 µg $Cr.L^{-1}$; Van der Weijden and Reith 1982). Since Cr has not been proved essential for aquatic organisms, the main concern with aqueous Cr is the prevention of toxicity, resulting principally from the dumping of Cr-bearing wastes into water.

2.1 Cr SPECIATION IN WATER

Cr can be present in water as CrIII and CrVI. In well-oxygenated water CrIII is slowly ($k \approx 3.5 \times 10^{-10}$ $mol.L^{-1}.a^{-1}$) converted to CrVI, but the presence of MnO_2 greatly increases the rate of oxidation ($k' \approx 2 \times 10^5$ $L.mol^{-1}.a^{-1}$; Van der Weijden and Reith 1982). Acidic and anoxic conditions as well as the presence of oxidizable organic matter favor the reduction of CrVI to CrIII. Thus CrVI predominates in oxygenated seawater (low in organic matter and relatively high pH) but not in anoxic bottom layers (Oshida 1977; Cranston 1980). CrIII is more likely to predominate in freshwater (higher in organic matter and relatively lower pH) unless large amounts of CrVI have been added, overloading the reducing capacity of the system.

Whereas CrVI is not adsorbed or complexed to any significant degree in aquatic ecosystems, CrIII adsorbs onto mineral surfaces or forms complexes with organic matter. Therefore total CrVI is probably a better indicator of CrVI availability than total CrIII is of CrIII availability. Guglielmucci et al. (1981) developed an analytical

procedure for determining the following Cr fractions in natural waters: total Cr, particulate Cr, dissolved Cr, complexed Cr (low and high molecular weight) and exchangeable and nonexchangeable Cr.

2.2 EFFECTS ON MICROORGANISMS

Microorganisms are an important first link in aquatic food chains. Although there is no evidence for Cr biomagnification (see Section 2.5) along the aquatic food chain, organisms can bioaccumulate Cr to levels that affect their ability to survive and reproduce. Table 1 lists some low-level criteria for Cr in microorganisms. Phytoplancton and algae appear to be most sensitive (toxic thresholds ≈ 0.01-0.1 mg $CrVI.L^{-1}$) while bacteria and viruses appear to be the most resistant to inactivation by Cr. Usually CrVI was more toxic, although dissolved (i.e. available) CrIII also had an appreciable toxicity, especially at low concentrations of adsorbing and complexing species.

2.3 EFFECTS ON INVERTEBRATES

Table 2 summarizes some effects of Cr on invertebrates. Among adult invertebrates, the Daphnids were the most sensitive to CrVI toxicity (24 h LC_{50} ≈ 0.4 mg $CrVI.L^{-1}$) while starfish, prawns and sea urchins were more tolerant (toxic concentrations ≥ 5 mg $CrVI.L^{-1}$). Development and reproduction were much more sensitive to CrVI (inhibitory thresholds in the range 0.01-0.05 mg $CrVI.L^{-1}$) and even to CrIII (0.5 mg $CrIII.L^{-1}$ for immobilized sea urchin sperm). It would appear that reproduction, development and predator avoidance are better measures of Cr ecotoxicity than mortality tests which may ignore factors that may eventually lead to species extinction in Cr-contaminated environments.

2.4 EFFECTS ON FISH

Table 3 contains representative data on the effects of low-level exposure to CrIII and CrVI on fish. Trout and other salmonids are the most Cr-sensitive species (deleterious effect threshold ≈ 0.1 mg $CrVI.L^{-1}$) while carp, bluegill and fathead minnow are up to 100 times more Cr-resistant. In addition to species of fish, a number of other factors influence the apparent Cr toxicity as outlined below.

2.4.1 INFLUENCE OF OXIDATION STATE

CrIII *per se* is of little toxicological concern in most aquatic ecosystems because adsorption and complexation render its availability very low. Nevertheless, in situations where there are few adsorbing or complexing species (e.g. seawater or nonturbid freshwater) not only does Cr^{3+} have a considerable lifetime but also it is available and toxic (NRCC 1976; Van der Weijden and Reith 1982; Stevens and

Chapman 1984). Furthermore, dissolved Cr^{3+} can be oxidized by MnO_2 under aerobic conditions to the more toxic CrVI.

CrVI is generally more available than CrIII (i.e. a greater fraction remains in solution) and it crosses biological membranes much more easily than CrIII (NRCC 1976). Thus CrVI, depending on the pH (see below, Section 2.4.2), can either cross gill membranes and produce systematic damage (e.g. renal damage affecting Na^+/K^+ balance in fish) or oxidize gill mucus and protein and become transformed to CrIII which then may interfere with gill functioning (van der Putte et al. 1981a).

2.4.2 INFLUENCE OF pH

van der Putte et al. (1981a) showed that when rainbow trout were exposed to CrVI, more Cr accumulated in the body than in the gills at pH 7.8 while the reverse was true at pH 6.5. It was postulated that at pH > 7, the CrVI toxicity resulted from effects on accumulator organs (liver, kidney; see Rewholdt et al. 1976, Ten Holder and Hogendoorn-Roozemond 1978 and van der Putte et al. 1981a for details of Cr uptake and distribution). However, at pH < 7, CrVI toxicity resulted from interaction with the gills, thereby leading to osmoregulatory and respiratory impairment (van der Putte et al. 1982). This is reasonable because CrVI is more strongly oxidizing under acidic conditions and therefore would be more likely to oxidize the first organic matter with which it came into contact — in this case the gill epithelium and mucus. With rainbow trout of a given weight, the 96-h LC_{50} was about 3 times greater at pH 7.8 than at pH 6.5 (i.e. greater mortality was observed at pH 6.5).

2.4.3 INFLUENCE OF WEIGHT

van der Putte et al. (1981b) found that at a given pH, CrVI toxicity to rainbow trout decreased with increasing weight: 0.2-g fish had 5 to 6 times the mortality of 25-g fish. In general, the eggs and adult fish were more Cr-resistant than the young fry.

2.4.4 INFLUENCE OF WATER HARDNESS

Increasing water hardness from 20 to 320 mg $CaCO_3.L^{-1}$ generally decreases the acute toxicity of CrVI by about one order of magnitude (EIFAC 1983).

2.4.5 INFLUENCE OF SALINITY

Changes in salinity (e.g. in estuarine environments) can act as an additional stress on an organism; since CrVI produces osmoregulatory dysfunction, this stress can lead to increased mortality at a given level of CrVI (EIFAC 1983; see also Table 3: Sugatt 1980b).

2.4.6 INFLUENCE OF OTHER TOXIC SUBSTANCES

Mixtures of Ni and Cr were reported to have more-than-additive effects on fish (EIFAC 1983) whereas CrVI and HCN had less-than-additive effects in the concentration range 0.02-0.08 mg $HCN.L^{-1}$ and 0.02-3.0 mg $CrVI.L^{-1}$ (Broderius and Smith 1979).

2.5 BIOACCUMULATION, BIOMAGNIFICATION

Fish accumulate Cr mostly in the gills, liver and kidney; muscle has little capacity for accumulating Cr (EIFAC 1983). Fish die before accumulating toxic levels of Cr in their edible tissues. This is also true for organisms below fish in the food chain, i.e. Cr does not biomagnify (EIFAC 1983).

2.6 GUIDELINES

Tentative guidelines have been set for Cr in aquatic environments (EIFAC 1983). These focus on survival of salmonid (Cr-sensitive) and non-salmonid (Cr-resistant) species:

salmonids : "The mean aqueous concentration of 'soluble' (passes 0.45 µm filter) chromium should not exceed 0.025 $mg.L^{-1}$ and the 95 percentile should not exceed 0.1 $mg.L^{-1}$."

non-salmonids: "The mean concentration of chromium should not exceed 0.1 $mg.L^{-1}$ and the 95 percentile should not exceed 0.4 $mg.L^{-1}$."

The non-salmonid guideline was considered not to protect the more sensitive species of invertebrates, and thus it was proposed that the salmonid guideline should also be applied to non-salmonid waters in order to preserve the food chain (EIFAC 1983).

3.0 Cr AND TERRESTRIAL PLANTS

Cr does not appear to be an essential element for plants (Zaccheo *et al.* 1982). Crops growing in uncontaminated soils contain ≤ 5-500 $\mu g\ Cr.kg^{-1}$ (dry weight) (Cary *et al.* 1977) and no deficiency symptoms were identified at the lower Cr concentrations.

In general, plants become stunted and die before they can accumulate in their edible tissues amounts of Cr that would be toxic to consumer organisms (NRCC 1976; Cary *et al.* 1977). Therefore the two main concerns with Cr in terrestrial food chains are:

(i) that toxicity of Cr to crops be prevented; and
(ii) that sufficient amounts of this essential element be provided in the diet to prevent Cr deficiency in animals and humans.

3.1 Cr SPECIATION IN SOIL

CrIII is cationic and therefore binds to clay particles, soil organic matter, metal oxyhydroxides and other negatively charged moieties. Anions of organic acids may complex the CrIII, although if the complex is charged, then it will remain in the soil solution. CrVI is anionic and therefore does not interact with clay or organic matter, but rather remains as the mobile free anion unless it forms a low-solubility complex with a cation such as Pb^{2+} (NRCC 1976).

Not only is CrVI reduced to CrIII by organic matter and other reducing substances, e.g. FeII (James and Bartlett 1983b), but conversely, CrIII (especially when present as a soluble organic complex) is oxidized by Mn oxides in aerobic soils to form CrVI (Bartlett and James 1979). However, insoluble CrIII precipitates are only sparingly available for oxidation to CrVI. The significance of these reactions under field conditions is not known; if the laboratory results of Bartlett and James (1979) are valid, then 'average' aerated soils have the capacity to convert up to 0.01 mg $Cr.kg^{-1}$ of soil from the III to the VI oxidation state and high-Mn soils may convert up to 1.2 mg $Cr.kg^{-1}$ of soil.

3.2 AVAILABILITY OF DIFFERENT Cr SPECIES FOR UPTAKE BY PLANTS

In nutrient solution CrIII and CrVI are equally available to plant roots (Lahouti and Peterson 1979), even though CrVI uptake appears to be active while that of CrIII appears to be passive (Skeffington *et al.* 1976). In soils, however, the availability of the cation CrIII decreases dramatically as the cation exchange capacity (CEC) increases, while that of the anionic CrVI remains relatively unchanged (although increased levels of organic matter, which strongly contribute to the soil CEC, may reduce CrVI to CrIII). CrIII-organic complexes (e.g. Cr oxalate, tartrate, citrate) and chelates (Cr-EDTA) may remain in solution for considerable periods of time (James and Bartlett 1983a) but they are poorly absorbed by plant roots (Cary *et al.* 1977). As mentioned above, these CrIII complexes may be oxidized to CrVI by MnO_2 in the soil.

3.3 Cr SPECIATION IN PLANTS

There is evidence that, at least in barley roots, CrIII is partly (≈ 0.5%) converted by an energy-requiring process to CrVI (Skeffington *et al.* 1976). CrVI is somewhat more mobile than CrIII in plant tissues; however, neither CrVI nor CrIII are translocated to any great extent either from roots to shoots or vice versa (Skeffington *et al.* 1976; Cary *et al.* 1977; Parr and Taylor 1980). The CrVI in plants is assumed to be present in simple anionic form while CrIII forms a number of complexes such as the oxalate (Cary *et al.* 1977), the

"glucose-tolerance-factor" (or GTF; Mertz 1979) and others yet to be characterized (e.g. see Starich and Blincoe 1982, 1983, and Section 4.1).

3.4 TOXIC EFFECTS OF Cr ON PLANTS

Since CrIII in the soil as well as that absorbed into roots may be partly converted into CrVI and vice versa, it is difficult to distinguish the individual toxicities of CrIII and CrVI. Nevertheless it is possible to make some generalizations:

(i) in solution culture, the toxic threshold for CrIII or CrVI is in the range of 1-5 $mg.kg^{-1}$ (NRCC 1976);
(ii) as the CEC of the growth medium increases, the toxic threshold for CrIII increases to 5-10 $mg.kg^{-1}$ for sand, and to 5000 $mg.kg^{-1}$ for compost (mostly organic matter) (NRCC 1976; Hanus 1980; McGrath 1982); and
(iii) the threshold for CrVI toxicity is affected only to the extent that organic matter reduces CrVI to CrIII.

Because the maximum reported conversion of CrIII to CrVI by soil Mn was 1.2 $mg.kg^{-1}$ (Bartlett and James 1979), it is likely that in some soils the toxic CrVI threshold may be approached or exceeded if soluble CrIII only is added. Furthermore, CrIII itself becomes toxic to plants under conditions that increase its availability in the soil (increasing acidity, decreasing organic content). Therefore, CrIII may not be as innocuous as previously supposed, and this calls for a reappraisal of agricultural practices that add large amounts of Cr to croplands.

3.5 PREVENTING Cr DEPLETION IN TERRESTRIAL FOOD CHAINS

Measures taken to prevent Cr toxicity to crops should be designed to avoid a depletion of this essential element from the food supply. Cary et al. (1977) studied ways of increasing Cr levels in plants without reducing crop yields. They found that Cr^{3+} and its complexes were poorly taken up but that low levels of CrVI (0.05-0.6 $mg.L^{-1}$ of nutrient solution) could sufficiently increase Cr levels, especially in leafy vegetables (lettuce, spinach), without decreasing yields. This level of CrVI may be achieved by the natural conversion of CrIII to CrVI by the Mn in aerobic soil, i.e. additions of CrVI may be unnecessary.

A more important question that remains to be answered is whether the Cr species formed by supplementing plants with Cr are nutritionally useful to animals and humans. This, as well as the Cr adequacy of present diets, must be known before Cr supplementation of soil is undertaken.

4.0 Cr IN FOOD

4.1 Cr SPECIATION

Very little is known about the Cr species present in most foods even though there is almost a 50-fold difference in gastrointestinal uptake between Cr^{3+} and GTF-Cr (GTF = glucose tolerance factor). Toepfer et al. (1973) used an ethanol extraction procedure to estimate GTF levels in food, although other species in addition to GTF may have been measured.

Starich and Blincoe (1983) used gel filtration to isolate Cr species derived from plant material. In alfalfa they found a Cr complex which had a molecular weight of ≈2600 (GTF molecular weight ≈400) and which was absorbed by rats even more readily than GTF. The in vivo biological activity of this complex was not determined but it appeared that most higher plants contain similar Cr complexes.

Although brewer's yeast contains relatively high levels of GTF-Cr, most commercial beers have very little Cr that is biologically active (Anderson and Bryden 1983). Of the 0.5-60 ng $Cr.L^{-1}$ in beer, only a small portion (max. 7 $ng.L^{-1}$) comes from the natural ingredients whereas the rest comes from the leaching of stainless steel tanks and piping used in the fermentation and bottling processes. Similarly, Offenbacher and Pi-Sunyer (1983) found that most of the Cr in fruit juice likely comes from stainless steel holding vats. It has also been found that hop extract can inhibit the insulin potentiating activity of GTF (Anderson and Bryden 1983). Other workers reported much higher Cr levels in beer (≈300 $\mu g.L^{-1}$) and in urine (≈450 $\mu g.L^{-1}$) but neither the biological activity nor the speciation was investigated (Anderson and Bryden 1983).

4.2 DAILY INTAKE

Vobecky et al. (1979) measured Cr levels in Canadian infant formulae and in baby foods. Infants ingested 30-60 $\mu g\ Cr.d^{-1}$, and breast-fed infants received slightly more Cr than formula-fed infants. (Note: in Finland, a country with lower environmental levels of Cr, apparently healthy breast-fed infants ingested only 0.3 $\mu g\ Cr.d^{-1}$; Kumpulainen and Vuori 1980). On a $\mu g.kg$ body-$weight^{-1}$ basis, the daily Cr intake was 14 at age 1 month and 4-7 above 3 months. This compares with an accepted value of 1-2 $\mu g.kg^{-1}.d^{-1}$ for adults.

4.3 EFFECT OF FOOD PROCESSING

Kumpulainen and Koivistoinen (1977) found that of the 40-55 $\mu g\ Cr.kg^{-1}$ (dw) in whole wheat or rye, ≈25% was lost during the production of "whole grain" flour while ≈50% was lost when white flour was produced. Similar results were obtained by Schroeder (1971). Since both GTF-Cr (Toepfer et al. 1973) and the Cr complex found in higher plants (Starich and Blincoe 1983) are water soluble, canning or blanching and freezing of sliced fruits and vegetables may result in

significant Cr loss to the processing water; however, no studies were found that provided quantitative estimates of this loss.

Stainless steel processing equipment may add considerably to the Cr content of foods, particularly acidic foods (Offenbacher and Pi-Sunyer 1983). However, it seems unlikely that Cr from this source is as available (or biologically useful) as the naturally occurring Cr complexes found in plants; by the same token, this factor is not likely to pose a significant risk to individuals consuming the food.

5.0 EFFECTS IN MAMMALS

The biological activity of Cr in mammals (as in other organisms) is sharply divided according to its oxidation state. CrIII in the form of an organic complex is an essential cofactor for the hormone insulin, but CrVI produces oxidative damage and in some cases cancer (Mertz 1983). The critical concern with Cr in mammals, then, is to provide sufficient CrIII for optimum metabolic functioning while minimizing CrVI exposure.

5.1 Cr METABOLISM, ESSENTIALITY AND DEFICIENCY

5.1.1 DATA QUALITY

Recent advances in analytical methodology showed that contamination (from reagent blanks and from stainless steel apparatus) and spectral interferences (necessitating the use of background correction) often resulted in reported serum and urine Cr levels that were a factor of 10-100 too high (Vanderlinde et al. 1979; Mertz 1979; Versieck et al. 1979; Verch et al. 1983). Thus, many of the pre-1978 data on low levels (≤ 1 µg $Cr.kg^{-1}$) of Cr in biological materials may not be valid. As much as possible, this has been taken into account in selecting the quantitative data quoted below. In assessing earlier data it is considered that trends or ratios of Cr concentrations are less likely to be erroneous than the individual absolute values.

5.1.2 Cr ESSENTIALITY

A specific organic complex of CrIII is an essential cofactor in the binding of serum insulin to cell receptor sites which regulate the transport of glucose and some other six-carbon sugars (Mirsky et al. 1980) into the cell (Mertz 1981, 1982). There is evidence that the biologically active Cr species is a dinicotinic acid-glutathione complex of CrIII called the "glucose tolerance factor" (GTF); however, it has not yet been successfully isolated and characterized (Mertz 1982).

The GTF acts only through insulin to maintain effective glucose homeostasis. Thus not only are excessive serum glucose levels (hyperglycemia) reduced by GTF-insulin, but the more effective

functioning of lower levels of insulin also prevents the secretion of too much insulin in response to a given amount of glucose leading to abnormally low serum glucose levels, i.e. hypoglycemia (Polansky et al. 1981; Anderson et al. 1983).

The human requirement for Cr (as GTF) is lower than for any trace element except Co in vitamin B12 (Mertz 1983). GTF or very similar Cr complexes are present in a number of foods (Toepfer et al. 1973) and these complexes are absorbed 10 to 25 times more readily than inorganic Cr^{3+} (Saner 1980). The highest levels of GTF are found in brewer's yeast; but, curiously enough, clarified beer is not a source of GTF (Anderson and Bryden 1983).

GTF can also be synthesized in vivo from absorbed inorganic Cr^{3+}; however, the site of synthesis is not yet known (Mertz 1979). It appears, therefore, that either 8-10 µg $Cr.d^{-1}$ as GTF or 50-200 µg $Cr^{3+}.d^{-1}$ in the diet adequately fill Cr metabolic requirements (Mertz 1979; Offenbacher and Pi-Sunyer 1980). Thus, the nutritional adequacy of a diet depends not only on the amounts of CrIII and GTF in the food but also on the relative ability of the consumer organism to synthesize GTF from Cr^{3+}.

5.1.3 NORMAL METABOLISM

Table 4 lists some important metabolic parameters for Cr. In vivo, Cr is present almost exclusively as a mixture of CrIII species. This is because CrVI, unless present at high concentration, is rapidly and quantitatively reduced to CrIII in vivo (Saner 1980). The problem is that before it is reduced, CrVI (because of its greater membrane permeability) may enter metabolic compartments not normally accessible to CrIII.

When inorganic CrIII is absorbed from the gastrointestinal tract (mainly from the midsection of the small intestine; Saner 1980) it appears that some of it is used to synthesize GTF in vivo because purely inorganic CrIII supplements can reverse a GTF deficiency (although at a slower rate than GTF itself, e.g. 2-3 weeks vs. several days; (Mertz 1979). GTF appears to be absorbed unchanged and is utilized as such in the body; however, ≈25% of GTF is absorbed, compared with only 0.5-1% of Cr^{3+} (Mertz 1983). Thus 8-10 µg GTF was found to have the same biological potency as 200 µg Cr^{3+} (Mertz 1983).

In the blood, inorganic CrIII not converted to GTF binds to serum transferrin (a Fe-transport protein) and probably follows some Fe pathways (Saner 1980). Low-molecular-weight complexes also help regulate Cr metabolism and play an important role in limiting Cr toxicity (Wada et al. 1983a, b) as well as in promoting its excretion (Norseth et al. 1982; Kayne et al. 1982); at present, however, these complexes are poorly characterized.

CrVI species rapidly enter red blood cells where they are reduced to CrIII and remain strongly bound to hemoglobin. In contrast, CrIII species are rapidly cleared from the bloodstream and are stored mostly in soft tissues (the liver may be the main storage site for biologically active Cr) where they are no longer in equilibrium with Cr in the blood (Saner 1980). Cr is returned to the bloodstream as GTF only in response to increased levels of plasma insulin, which in turn is a response to increased levels of blood glucose. The maximum increase in serum GTF occurs 30-120 minutes after the administration of glucose (Mertz 1979).

The low-molecular-weight Cr species in the blood are also filtered at the renal glomerulus and are only partially resorbed at the proximal renal tubule, so that some appear in the urine. Therefore, each time a glucose load stimulates insulin and consequent GTF secretion into the bloodstream, some of this Cr is lost in the urine.

In normal persons, who are able to synthesize and secrete insulin and mobilize GTF in response to insulin, the changes in plasma Cr (ΔCr B) and urinary Cr (ΔCr U) during 2-3 hours after a glucose dose are the best measures of *in vivo* Cr status (Mertz 1979). This is because under fasting conditions, neither blood Cr nor urinary Cr is in equilibrium with body stores. Also, hair may not reliably indicate Cr status because deficiencies in other nutrients, e.g. Zn and protein, which often occur with Cr deficiency, may decrease the rate of hair growth and mask a decreased rate of Cr incorporation into hair (Mertz 1979). It should be noted that heavy supplementation with Cr^{3+} may mask the ΔCr B and ΔCr U responses by increasing non-GTF Cr levels in blood and urine to such an extent that the additional increase due to GTF secretion in response to glucose is not noticeable (see Anderson *et al.* 1982b for a possible example). The final proof that an individual is deficient in Cr is obtained when there is improved glucose tolerance or reduction of elevated insulin levels after supplementation with Cr^{3+} or, preferably, GTF (Mertz 1979).

Table 4 indicates that for the 'average' adult North American or European, the diet supplies adequate Cr to meet normal metabolic requirements. Depending on the rate of absorption from the respiratory tract, inhalation may contribute significantly to daily Cr absorption (see Table 4, Wada *et al.* 1983a; Kiilunen *et al.* 1983). Nevertheless, as Mertz (1979) pointed out, as many as 33% of otherwise nutritionally adequate diets may supply less than the estimated minimum daily requirement of 50 μg $Cr^{3+}.d^{-1}$ (or its equivalent in more readily absorbed GTF).

5.1.4 Cr IN PREGNANCY

Simple Cr^{3+} salts do not cross the placental barrier to any significant extent, but GTF-Cr is readily transferred from mother to fetus, especially during the third trimester. Thus, full-term infants have higher levels of Cr than premature infants and perhaps even higher levels than the mother (Gurson 1977).

Injected CrVI crosses the placental barrier (Danielsson et al. 1982), but oral doses are toxic to the mother before the fetus is affected. No information was found concerning the transfer and possible effects on the fetus of CrVI inhaled by the mother.

5.1.5 Cr DEFICIENCY (see also Section 5.6.2)

Because of its low rate of gastrointestinal absorption and low toxicity, CrIII is toxic only when large amounts are injected into the body (Mertz 1983), in which case it actually inhibits insulin secretion and produces hyperglycemia (Ghafghazi et al. 1979, 1980). However, CrIII deficiency can produce glucose intolerance (i.e. inability to clear glucose from the bloodstream), and eventually a syndrome indistinguishable from diabetes mellitus (Lim et al. 1983).

Mertz (1982) outlined the sequence of events leading to pronounced Cr deficiency in mammals. In the first stage (compensated deficiency), increased insulin secretion compensates for a decreased concentration of binding cofactor so that all insulin-dependent functions are maintained intact. However, increased concentrations of insulin stimulate increased Cr secretion from already deficient storage sites, paradoxically resulting in elevated levels of fasting blood Cr and increased excretion of Cr in urine. This positive feedback eventually leads to a second phase (functional deficiency) in which fundamental metabolic disorders become noticeable through, for example, abnormal glucose tolerance and accompanying disturbance of lipid metabolism (cells unable to absorb sufficient glucose shift to lipids to meet their energy requirements; Boyle et al. 1977). In the final phase (pronounced deficiency) there is marked resistance to the action of insulin, which might lead to exhaustion of pancreatic insulin production and the development of insulin-dependent diabetes mellitus.

The above sequence of events does not imply that Cr deficiency is the dominant factor causing diabetes mellitus, but rather is one nutritional factor that can be involved in the development of the disease (Mertz 1982). (Other nutritional factors involved may be Cu, Se, Mg and the type of carbohydrate ingested; see Magnesium 2(4), 1983; Fields et al. 1984.) Conversely, Cr should be considered an essential micronutrient, required to act with insulin for maintenance of normal glucose tolerance (and therefore normal lipid metabolism) and not a drug for treatment of disturbances of carbohydrate metabolism (Mertz 1976). Nevertheless, "chromium deficiency should be considered in all clinical situations where an unexplained insulin resistance develops in patients. Chromium deficiency should also be considered as one of several nutritional factors that influence three recognized risk factors for public health problems of cardiovascular diseases, impaired glucose tolerance, elevated circulating insulin levels, and elevated serum cholesterol" (Mertz 1982).

Pronounced Cr deficiency is unlikely to occur in humans consuming balanced diets (Saner 1980), but evidence of increased

excretion or low absorption and utilization leading to functional deficiency was found in some (see Table 5), but not all, situations (see Rabinowitz et al. 1983).

5.1.5.1 Cr Deficiency in Pregnancy

Substantial quantities of Cr are mobilized from maternal stores for transfer to the fetus during the last trimester of pregnancy (Gurson 1977). There is evidence that this may lead to a temporary Cr deficiency in the mother:

(i) hair Cr decreases by an average 26% as the pregnancy progresses and, depending on diet and time between pregnancies, may subsequently revert to pre-childbearing levels (Saner 1981a, b);
(ii) fasting serum Cr levels increase by approximately 50% in the last 10 weeks of pregnancy (Conner and Cassady 1978, 1979) and the daily Cr excretion in urine also increases (Saner 1981b), as would be expected in first-stage deficiency;
(iii) the normal rise in serum Cr after glucose administration is often absent in late pregnancy; however, the insulin response to glucose is greatly increased (Saner 1980) as would be expected in first-stage deficiency;
(iv) in some women, the glucose clearance rate from blood falls by approximately 40% by the third trimester (Gurson 1977), as would be expected in second-stage deficiency.

5.1.5.2 Cr Deficiency in Aging

Aging is associated with gradual depletion of Cr stores in the body, more likely because of poor diet rather than a decreased rate of absorption. Regardless of the cause, it appears that Cr^{3+} or GTF supplements do improve glucose tolerance and lower serum cholesterol levels in 40-50% of those with abnormal values (Gurson 1977; Offenbacher and Pi-Sunyer 1980; see Table 5); some studies, however, reported completely negative results (Rabinowitz et al. 1983). Vallerand et al. (1984) indicated that exercise was effective in minimizing Cr loss with age in rats.

5.1.5.3 Cr Deficiency in Diabetics

Diabetes can occur despite adequate body stores of GTF-Cr. In this case the primary cause of the diabetes could be either an effect on insulin production and release, or some other aspect of carbohydrate metabolism not immediately involving Cr (e.g. see Pierluissi and Campbell 1980; Anon. 1983). Injection of insulin to compensate for reduced endogenous production may, however, increase Cr excretion and produce a Cr deficiency secondary to diabetes. Since Cr is essential for insulin functioning, the Cr deficiency could lead to further impairment of glucose tolerance but this secondary effect would be

reversible by Cr supplementation. GTF-Cr supplementation may therefore reduce the insulin requirement in some diabetics.

Animal studies have shown that pronounced Cr deficiency (Lim et al. 1983) or an inability to convert inorganic Cr into GTF (Doisy et al. 1973) can be a cause and not just a consequence of diabetes. A number of human studies showed that Cr supplementation improved glucose tolerance in diabetics and hyperglycemics (Gurson 1977; Liu and Morris 1978), but this may only correct a Cr deficiency secondary to diabetes. However, studies of Cr metabolic disturbances in nondiabetic relatives of diabetics (Gurson and Saner 1978) and in "healthy" persons having normal glucose tolerance (Liu and Morris 1978; Liu and Abernathy 1982; Anderson et al. 1983) support the hypothesis that Cr can be a primary cause of diabetes (especially late-onset or adult diabetes) in some humans. Similarly, diseases characterized by abnormally low Cr retention (e.g. hemochromatosis, Sargent et al. 1979; Lim et al. 1983) are associated with above-average rates of diabetes incidence.

5.1.5.4 Cr Deficiency in Atherosclerosis

Cr deficiency starves insulin-dependent cells by reducing their ability to absorb glucose. As a consequence, these cells shift to lipids as an energy source and lipid stores are mobilized into the bloodstream to meet this need. The results are abnormally high levels of serum cholesterol and lipids (Boyle et al. 1977), both of which are factors associated with a high risk of atherosclerotic cardiovascular disease. The elevation of serum insulin levels (both in the fasting state and in response to glucose) that results from Cr deficiency (Mertz 1979) may be the first of a sequence of events leading to atherosclerosis.

Excess insulin is injurious to arterial tissue because: (i) it leads to a proliferation of smooth muscle cells (Saner 1980) causing deformation and constriction of the blood vessels; (ii) it stimulates hepatic synthesis of very low density lipoprotein which is hypothesized to carry lipid and cholesterol into the vascular tissue from the blood (Boyle et al. 1977); and (iii) it suppresses the breakdown or removal of lipids in the artery wall leading to buildup of fatty deposits (Boyle et al. 1977). Thus, atherosclerosis may occur secondary to Cr deficiency and compensatory insulin overproduction, especially in populations with high intakes of refined sugar. A number of studies with humans have shown that Cr^{3+} or GTF supplementation not only reduces excessively high serum cholesterol levels (Nash et al. 1979; Offenbacher and Pi-Sunyer 1980; Elwood et al. 1982) and increases the levels of high density lipoprotein (thought to be a protective factor acting to remove cholesterol from vascular tissues; Riales and Albrink 1981) but also may even act to reduce serum cholesterol values in the "normal" range (Nash et al. 1979; Elwood et al. 1982). Abraham et al. (1980, 1982) reported that intraperitoneal injections of potassium chromate (for each animal, 5.3 µg $CrVI.d^{-1}$ for 30 weeks) were effective in reversing cholesterol-induced atherosclerosis in rabbits. The active agent was probably CrIII

formed by *in vivo* reduction of CrVI. Higher doses of CrVI (170 µg CrVI. kg BW^{-1}, orally for 3-6 months) were noted to be cardiotoxic (Magomedov 1973).

5.1.5.5 Cr Nutrition and Supplementation

It is recognized that a number of otherwise acceptable diets may be Cr deficient (Mertz 1979) and that the carbohydrate and lipid metabolism of certain subgroups of the population respond positively to Cr supplementation. Nevertheless, Cr supplementation without careful clinical monitoring of carbohydrate and lipid metabolism is not to be recommended. This is especially true in those who either receive insulin injections or have elevated levels of endogeneous insulin: sudden increases in the response to insulin could have catastrophic results by causing sudden and severe hypoglycemia.

5.2 Cr AND CANCER

Cr-induced cancer results primarily if not exclusively from occupational exposure to CrVI aerosols. Epidemiological studies indicate that the primary site of CrVI carcinogenic activity is the respiratory tract, although metastases can affect other tissues as well. There have been no reports of cancer caused by ingested CrVI, probably because CrVI is rapidly reduced to CrIII in acidic gastric juice.

5.2.1 EPIDEMIOLOGICAL STUDIES

In a comprehensive review, Hayes (1980) presented the following assessment of Cr occupational carcinogenesis:

Chrome refractory industry - insufficient data for assessment

Chromate-producing industry - definite link between high mortality from lung cancer and exposure to CrVI

Chromate pigment production and use - definite link between moderately increased incidence of lung cancer and CrVI exposure

Chrome-plating industry - some evidence supporting a causal link between CrVI exposure and a small increase in lung-cancer incidence

Ferrochrome alloy production - data do not consistently point to a causal link between Cr and cancer

More recent research supports the link between CrVI exposure and respiratory cancer in chrome pigment production and use (Dalager *et al.* 1980; Sheffet *et al.* 1982; Langard and Vigander 1983) and in chrome plating (Franchini *et al.* 1983; i.e. among "hard" chrome platers but not

"bright" chrome platers). Recent results for the ferrochrome industry are suggestive of a link but not conclusive (Langard et al. 1980; Axelsson et al. 1980). Welding fumes contain CrVI (as well as a number of irritants and possible carcinogens) and thus are also suspect (Hedenstedt et al. 1977; Gray et al. 1983).

From the physical and chemical characteristics of Cr compounds used in the above-mentioned industries it was possible to make the following generalizations on the carcinogenic activity of different Cr compounds:

(i) intermediate products of the chromate chemical production, particularly the roast residue, have been shown to be carcinogenic;
(ii) trivalent compounds appear not to be carcinogenic, although their effects upon in vitro DNA synthesis and upon chromosome structure and their mutagenicity at high concentrations need further investigation;
(iii) medium-solubility hexavalent chromates have consistently been shown to be carcinogenic;
(iv) the evidence for the carcinogenicity of the low solubility hexavalent products is not strong or consistent, although recent evidence indicates a carcinogenic role; and
(v) the highly soluble hexavalent compounds have not been shown to be carcinogenic, perhaps because of methodological difficulties, although they have recently been shown to cause chromosomal aberrations and mutations in experimental test systems (Hayes 1980).

5.2.2 EXPERIMENTAL STUDIES

Current research supports the hypothesis that CrVI produces chromosome damage and cancer because it can cross both the outer membrane and the nuclear membrane of the cell before being reduced to CrIII with consequent adverse affects on the DNA structure of the chromosomes (Bianchi et al. 1980, 1983; Sarto et al. 1980; Levis and Majone 1979). Thus it appears that while CrIII as GTF is essential for maintaining normal carbohydrate metabolism, CrIII, if delivered in excessive quantities into the nucleus, can be genotoxic (Okada et al. 1983).

The sensitivity of respiratory tissue to CrVI carcinogenesis probably results from two factors. First, airborne Cr particles deposit directly on the respiratory membranes and high localized concentrations of CrVI occur. Second, of all body tissues, respiratory tissues are least able to quantitatively reduce CrVI to CrIII in the cell cytosol so as to effectively limit the entry of Cr into the cell nucleus (Levis and Majone 1979; Bianchi et al. 1983). It is of interest to note that ascorbate, a mild reducing agent, reduced the genotoxicity of CrVI in cell cultures (Uyeki and Nishio 1983).

Lymphocytes appear to act as integrating *in vivo* monitors of exposure to genotoxic substances. Studies of lymphocytes from humans exposed to CrVI aerosols showed increased incidence of chromosome aberrations (≥10 μg CrVI.m^{-3} gave 3-5-fold increase; Paschin *et al.* 1982; see also Bigaliev 1981) and of sister chromatid exchange (≈50 μg CrVI.m^{-3} caused significant increase; Sarto *et al.* 1982).

5.3 EFFECTS ON LIVER

Even though the liver accumulates Cr, few studies have reported specific hepatic effects of either CrIII or CrVI.

Intraperitoneal injections of 2 mg.kg^{-1}.d^{-1} CrIII or CrVI for up to 6 weeks produced obvious adverse changes in rabbit liver histology (CrVI produced the more severe changes) even though morbidity and mortality were not changed significantly (Tandon *et al.* 1978). Injection (15 mg.kg^{-1}) or *in vitro* addition (1-100 μM) of CrIII or CrVI also affected the liver drug-metabolizing system (Snyder *et al.* 1977; Yonaha *et al.* 1980); however, the precise mechanisms of action are unknown.

Oral doses of CrVI (13 mg.kg BW^{-1} in rats; Kumar and Rana 1982) and of CrIII (20 mg.kg^{-1} of diet in turkeys; Steele and Rosebrough 1981) affected hepatic lipid metabolism resulting in increased fat deposition in the liver.

5.4 EFFECTS ON KIDNEYS

About 40% of the CrIII in normal plasma is ultrafilterable at the glomerulus and 60-95% of this is reabsorbed in the renal tubule. In contrast, less than 5% of CrIII-EDTA is reabsorbed (Donaldson and Rennert 1981). There is one report of death by hemolysis and acute renal failure produced by massive dermal exposure to acidic CrII sulfate (≈180 mg CrIII absorbed); however, this is an extreme case and it is not clear whether acid burns were not a contributory cause of death (Kelly *et al.* 1982).

CrVI is a recognized renal toxin affecting tubular epithelial cells and tubular transport processes (Kirschbaum *et al.* 1981). Accumulation of Cr in rat kidneys after repeated doses of CrVI (0.35 mg CrVI.kg^{-1}.d^{-1} 5 days per week for 8 months) produced vacuolar changes in the tubular epithelial cells (Berry *et al.* 1978). Cr was excreted only when the epithelial cells became necrotic. Although massive doses of CrVI (e.g. ingestion of several grams of $K_2Cr_2O_7$; Sharma *et al.* 1978) are required to produce renal failure, lower doses (e.g. airborne CrVI levels ≥ 10 μg.m^{-3} in chrome plating shops) can result in reversible elevation of urinary B_2 microglobulin (proteinuria) in the absence of significant Cd exposure (Lindberg and Vesterberg 1983). Welders of stainless steel are exposed to CrVI in welding fume but Littorin *et al.*

(1984) found that welders had a urinary protein concentration greater than that in a control group (urinary Cr of 6-11 $\mu g.g^{-1}$ creatinine vs. ~0.7 $\mu g.g^{-1}$ creatinine, respectively).

5.5 RESPIRATORY EFFECTS

5.5.1 IRRITATION AND INJURY

CrVI is corrosive and can injure any respiratory tissue it contacts. The following criteria were quoted in NRCC (1976):

0.05-0.1 mg $CrVI.m^{-3}$ - threshold for generalized bronchospasm
0.05 mg $CrVI.m^{-3}$ - high probability of injury to nasal tissues
0.01 mg $CrVI.m^{-3}$ - nasal irritation
0.0025 mg $CrVI.m^{-3}$ - asthmatic attacks in sensitized persons

Once an individual has become sensitized to CrVI, even CrIII inhalation may provoke asthmatic attacks (Novey et al. 1983); however, the threshold levels are not known.

5.5.2 ALVEOLAR MACROPHAGE INHIBITION

A number of in vitro studies showed that Cr-containing particulate matter decreased alveolar macrophage viability and thus might increase susceptibility to airborne infectious agents. A more recent study by Galvin and Oberg (1984) confirmed the in vitro work but showed that when a Cr solution was administered intratracheally, there was no significant effect on alveolar macrophage activity. Inhaled particulate matter containing leachable Cr may maintain higher local levels of Cr over longer periods and have an in vivo effect on the macrophages whereas Cr solutions may not.

5.5.3 CANCER (see Section 5.2)

5.6 EFFECTS ON REPRODUCTION

5.6.1 EFFECTS OF Cr EXCESS

5.6.1.1 In vitro studies

Bianchi et al. (1983) found that CrVI gave positive results in the following tests for genetic damage:

- DNA replication fidelity test
- Ames test (Salmonella)
- gene mutation test (hamster cells)
- sister chromatid exchange test
- cell transformation test

CrIII was not genetically active unless it was permitted to react directly with DNA in a cell-free system. This implies that CrVI is the only Cr species able to enter the cell in sufficient quantity to produce genotoxic effects but it is CrIII produced intracellularly from CrVI that is the ultimate genotoxic agent (Bianchi et al. 1983).

Mouse embryos cultured in Cr-containing solutions exhibited an increased rate of sister chromatid exchange and impaired cell division at CrVI concentrations ≥50 $\mu g.L^{-1}$ (Iijima et al. 1983). At 200 μg $CrVI.L^{-1}$ there was a significant increase in embryo mortality (Jacquet and Draye 1982).

5.6.1.2 In vivo studies

Intravenous injection of CrVI and CrIII into pregnant mice on day 13 of gestation resulted in 12% and 0.4% transfer respectively from maternal blood serum to fetuses (Danielsson et al. 1982). Again, adminstration of CrVI is more likely to deliver a toxic dose of Cr to the target (fetus) than CrIII. Hamsters, injected once intravenously with ≥2.5 mg $CrVI.kg^{-1}$ between days 12-15 of gestation, had an increased percent of abnormal fetuses and resorption (Gale 1978).

No studies were found in which excess oral or respiratory exposure to CrIII or CrVI produced impaired reproduction in mammals without producing overt systemic toxicity in the mother. Therefore it appears that the mammalian fetus is well protected from all but massive exposure to CrVI or CrIII.

5.6.2 EFFECTS OF Cr DEFICIENCY (see also Section 5.1.5)

Anderson and Polansky (1981) reported that feeding male rats a Cr-deficient diet (≤100 μg $Cr.kg\ diet^{-1}$) from weaning resulted in a 50% decrease in sperm count and a 75% decrease in fertility at age 8 months. The authors did not determine whether Cr repletion returned sperm counts to normal values. Cr also appears to be essential in females of avian species for maintaining normal egg albumen (Jensen et al. 1978; Jensen and Maurice 1980).

5.7 BIOCHEMICAL EFFECTS

5.7.1 ENERGY METABOLISM

In vitro studies show that CrVI and CrIII can, in principle, adversely affect energy metabolism. For example, CrVI (0.05 mM) decreased the conversion of ADP to ATP in cultured hamster fibroblasts. Furthermore, CrIII forms kinetically stable complexes with ATP resulting in inhibition of enzymes that require Mg-ATP (NRCC 1976).

5.7.2 NUCLEIC ACID METABOLISM

Section 5.6.1.1 outlined some of the genotoxic effects of high levels of CrVI and CrIII on DNA and chromosomes. Lower levels of Cr can also have pharmacological effects, e.g. intraperitoneally injected CrIII ($\geq$0.05 $mg.kg^{-1}$) specifically enhances RNA synthesis in mouse liver, possibly through binding to DNA and increasing its template activity by increasing the number of chain initiation sites (Okada *et al.* 1983).

5.7.3 BIOLOGICAL MEMBRANES

In vitro, CrIII interacts strongly with biological membranes (e.g. nerve axon membranes) and thus alters their ionic permeability. The mechanism of this effect may involve Cr-induced conformational changes of chemical groups on the membrane surface or Cr-catalyzed peroxidation of the protein-lipid membrane material (NRCC 1976).

5.7.4 CrVI-REDUCING MOLECULES

At physiological pH (7.4) CrVI reduction in cells is not expected to be random and nonselective; rather, only certain small molecules (ascorbate and thiols such as glutathione, cysteine) and macromolecules (hemoglobin, cytochrome P450, glutathione reductase, NADPH-cytochrome P450 reductase) are capable of reducing CrVI at a significant rate (Connett and Wetterhahn 1983).

5.7.5 TREATMENT OF CrVI POISONING

Ingestion of several grams of CrVI or absorption of several tenths of a gram via the skin produces systemic toxicity and eventual renal necrosis and failure. Schiffl *et al.* (1982) suggested the immediate use of aggressive peritoneal dialysis while Behari and Tandon (1980) investigated the use of polyaminocarboxylic acid chelators for removing Cr from tissues *in vivo*. However, the simplest and most effective method appears to be the immediate intravenous injection of 1-3 g ascorbate, which was successfully employed by Korallus *et al.* (1984) in treating a patient splashed with a CrO_3 solution.

5.8 CONTACT SENSITIVITY TO Cr

After nickel, Cr is the most common cause of occupational dermatitis (Polak 1983). Cr contact sensitivity was reviewed extensively by Polak (1983) and Burrows (1983b) and therefore only a few points will be mentioned here.

(i) The allergic response threshold for CrVI applied to the skin is as low as 10 $\mu g.L^{-1}$ (Polak 1983).

(ii) The solubility of the Cr salt and not the Cr oxidation state is the decisive factor determining whether there will be an allergic reaction (Polak 1983).

(iii) Oral doses of Cr (2.5 mg) produced flare-up reactions in about 10% of persons suffering from Cr hypersensitivity. Flare-up was minimized by removing high-Cr foods from the diet (Veien et al. 1983). [Note: possible induction of Cr deficiency was not considered.]

(iv) Exposure of skin to ultraviolet light decreased the Cr concentrations required to elicit a reaction in about 50% of Cr-sensitive individuals (Wahlberg and Wennersten 1977).

6.0 Cr ANALYSIS

Developments in sampling, sample handling and determination of Cr up to 1975 were reviewed in NRCC (1976). Parr (1977) reported that methodology for determination of low levels of Cr in environmental and biological samples yielded erratic results because of contamination, loss or interferences. Since then a number of methods have been developed for low-level Cr analysis (see Table 6). Major advances have been: the introduction of adequate background correction in atomic absorption spectrometry, the use of clean-room equipment and facilities to minimize contamination, and the introduction of chromatographic and other methods for determining Cr speciation. The possible existence of volatile Cr species in biological samples remains controversial (Shapcott et al. 1977; Versieck et al. 1979).

Table 1. Effects of Cr on aquatic microorganisms.

Organism	Cr level ($mg.L^{-1}$)	Cr species	Effect	Reference
Chlorella pyrenoidosa[a]	0.05	CrVI	growth inhibition	Frey et al. (1983)
estuarine phytoplankton	0.1	CrVI	total growth inhibition at 0.03°/oo salinity; little inhibition at 32.5°/oo salinity	ibid.
Ulothrix fimbriata[a]	0.01	CrVI	50% loss of chlorophyll	Bharti et al. (1979)
Chlorella sp.[a]	0.1	CrVI	decreased rate of photosynthesis	Stary et al. (1982); Meisch and Schmitt-Beckmann (1979)
Euglena gracilis	1.5	CrVI	delayed reproduction	Fasulo et al. (1982, 1983)
bacteria, viruses	1-10	CrVI/ CrIII	thresholds for inactivation of sensitive species	NRCC (1976)

[a]Alga.

Table 2. Effects of Cr on aquatic invertebrates.

Organism	Cr level ($mg.L^{-1}$)	Cr species	Effect	Reference
Acartia chausi[a]	4	CrVI	incr. mortality after 7 days	Moraitou-Apostolopoulou and Verriopoulos (1982)
" "	0.1	CrVI	decr. feeding rate	*ibid.*
insect larvae	0.1	CrVI	incr. mortality	Ramusino *et al.* (1981); Chaisemartin (1976)
"	2-50	CrIII	96-h LC_{50}	NRCC (1976)
marine polychaete worm	0.02-0.04	CrVI	threshold for impaired reproduction	Oshida and Word (1982);
"	50	CrIII	no effect	Oshida *et al.* (1981)
sea urchin embryo	2.5	CrVI	impaired development	Pagano *et al.* (1983)
sea urchin gametes	0.5	CrIII	sperm affected; inhib. fertilization	*ibid.*
starfish	1.7	CrVI	7-d LC_{50}	Oshida and Wright (1977)
prawn	5.	CrV	toxic threshold	NRCC (1976)
Daphnia pulex	0.05-0.1	CrVI	toxic threshold during molting	Lee and Buikema (1979)
Daphnia	0.05 (from birth)	CrVI	complete inhib. of reproduction	Trabalka and Gehrs (1977)
"	0.01	CrVI	partial inhibition of reproduction	*ibid.*
juvenile crayfish	tenfold incr. in muscle-Cr to 0.26 $mg.kg^{-1}$ (wet weight)	CrVI	decr. ability to avoid predators	Chaisemartin (1979)

[a]Marine planktonic copepod.

Table 3. Effects of Cr on fish.

Organism	Cr level[α] ($mg.L^{-1}$)	Cr species	Effect	Reference
rainbow trout	3.4	CrVI	96-h LC_{50} for 0.2 g fish at pH 6.5	van der Putte et al. (1981b)
rainbow trout	0.57	CrVI	96-h TLm at pH 6.9; hardness 155 $mg.L^{-1}$	Hogendoorn-Roozemond and Ten Holder (1978)
rainbow trout	2.5	CrVI	62% decr. in renal ATPase in 48 h	Kuhnert et al. (1976)
brook trout	0.35	CrVI	incr. mortality in young at pH 7-8 and 45 $mg.L^{-1}$ hardness	Benoit (1976)
"	0.01	CrVI	temporary growth lag in young	ibid.
juvenile coho salmon	0.2-0.5	CrVI	(i) impaired adaptation to salinity changes	Sugatt (1980a)
			(ii) impaired resistance to infection	Sugatt (1980b)
atlantic salmon (fry)	0.01-0.1	CrVI	MATC[β] based on mortality	Grande and Anderson (1983)
fathead minnow	1-4	CrVI	MATC based on mortality; pH 7.7, hardness 204 $mg.L^{-1}$	Pickering (1980)
"	0.02	CrVI	transient growth depression	ibid.
Channa punctatus	2.6	CrVI	altered carbohydrate metabolism; pH 7.2, hardness 160 $mg.L^{-1}$	Sastry and Tyagi (1982)
bluegill	0.05-2.4	CrVI	range for threshold concentration affecting locomotor activity	Ellgaard et al. (1978)
steelhead trout	0.089 (80-80% soluble)	CrIII	increased mortality of early life stages	Stevens and Chapman (1984)
rainbow trout	2.5 $mg.kg^{-1}$ diet	CrIII	improved growth	Tacon and Beveridge (1982)
	8.2 $mg.kg^{-1}$ diet	CrIII	depressed growth	ibid.
carp	100	CrIII	96-h LC_{50}	Wong et al. (1982)

[α] In water unless otherwise stated.

[β] MATC = maximum acceptable toxicant concentration.

Table 4. Normal metabolism of Cr in humans (data for adults unless otherwise indicated).

Daily intake - inhalation : 0.01 - 1 µg (α)
ingestion : adults : 60-80 µg; some ≤50 µg (β)
: infants : 0.3 µg in mother's milk (γ)
dermal : no data

Absorption rates - respiratory - low for simple CrIII salts (δ)
- significant for CrIII lignosulfonate complex (δ)
- high for CrVI (depends on solubility) (ε)
gastrointestinal - simple CrIII salts : 1% (0.4-4%) (β,ζ)
- GTF and similar CrIII complexes : 10-25% (ζ)
- CrVI : 2% (0.2-4%) (ζ)
dermal - CrIII : very low
- CrVI : 50-100 $\mu g.cm^{-2}.h^{-1}$ per unit molar concentration (η)

Daily absorption - from air : no data
from diet : ≥1 µg (0.6-4) (θ)
from skin : no data

Daily excretion of absorbed Cr - (95%) in urine : 0.2-1 µg (β,τ)
(≤5%) in feces : ≤0.01 µg (β)
hair and skin etc : no data

Estimated daily dietary requirement (intake) - as Cr^{3+} : 50-200 µg (ι)
as GTF : ~10 µg (ι)

Accumulator tissues - Cr^{3+} : liver, kidney, spleen, testes, bone (κ)
GTF : liver (κ)
CrVI : red blood cells, kidney (κ)
liver is probable depot of biologically active Cr (κ)

Levels in - red blood cells : 28 $\mu g.L^{-1}$ (λ)
blood serum : 0.2 $\mu g.L^{-1}$ (0.04-0.4) (μ)
urine : 0.5-1 $\mu g.L^{-1}$ (β)
hair : ≥200-500 $\mu g.kg^{-1}$ (κ)

Indicator of Cr status - change in serum Cr or urinary Cr after a glucose dose (normal = +30-40%) (β,ν)
absolute Cr levels in hair, serum and urine are not reliable (β)

Table 4. (Cont'd)

Kinetics	lag time for effect of Cr supplement on glucose tolerance (Cr^{3+}): 1-2 wk (ξ) 3 component clearance : t½ = 0.5-12 h (o) (whole-body basis) = 1-14 d (o) = 3-12 mo (o)
Placental transfer	GTF-Cr : readily transferred (β) simple Cr^{3+} salts : not measurably transferred (β) injected CrVI crosses placental barrier (π)
Interacting factors	decrease gastrointestinal absorption : Fe, Mn, Ti, Ca, phytate (ζ) increase gastrointestinal absorption : Fe or Zn deficiency, oxalate, glutamate, penicillamine (ζ,ρ) aggravate Cr deficiency - nutritional stress : protein deficiency, excess refined sugar (ζ) physical stress : heat, cold, infection, shock, strenuous exercise, repeated pregnancies (ζ) chemical stress : Fe and V are metabolic Cr antagonists (o) Zn deficiency impairs insulin release from pancreas (ζ) Cd - induced tubular dysfunction may impair Cr resorption (χ)

(α) Estimated from Bowen (1979), assuming 20 $m^3.d^{-1}$ inhalation and 50% deposition.
(β) Mertz (1979).
(γ) Kumpalainen and Vuori (1980).
(δ) Kiilunen et al. (1983).
(ε) Bragt and van Dura (1983).
(ζ) Saner (1980).
(η) Baranowska-Dutkiewicz (1981).
(θ) low range estimated assuming 1% absorption and all dietary Cr present as Cr^{3+}; high range estimated assuming 10% absorption and 50% dietary Cr present as GTF.
(ι) Mertz (1983).
(κ) Saner (1980).
(λ) Rabinowitz et al. (1980).
(μ) Versieck et al. (1979).
(ν) Gurson (1977).
(ξ) Mertz (1976).
(o) Lim et al. (1983), Sargent et al. (1979).
(π) Danielsson et al. (1982).
(ρ) Gonzalez-Vergara et al. (1981).
(σ) Hill (1979).
(τ) see Tola et al. (1977), Guillemin and Berode (1978) and Sjogren et al. (1983) for occupational data on the correlation of respiratory Cr exposure and urinary Cr e.g. 20 μg.CrVI.m^{-3} yields 15-35 μg Cr.L^{-1} of urine.
(χ) Donaldson and Rennert (1981).

Table 5. Studies of groups with reduced Cr retention or responding to Cr supplementation.

Key:
1-3 : low Cr retention.
4 : elderly having altered glucose and lipid metabolism.
5 : diabetics.
6-10 : adults with marginally to moderately impaired glucose or lipid metabolism.
11-15: 'normal' adults responding to Cr with improved glucose or lipid metabolism.

	Subjects	Observations	Reference
1	strenuously exercising men	24-h excretion of Cr almost doubled[a] (0.16 to 0.30 $\mu g.d^{-1}$)	Anderson et al. (1982a)
2	patients with excess-Fe storage disease	Cr retention reduced by 50%	Lim et al. (1983)
3	patients with excess-Fe storage disease (hemochromatosis)	decreased retention of absorbed Cr; higher incidence of diabetes in this group than in general population	Sargent et al. (1979)
4	elderly persons	11 $\mu g\ Cr.d^{-1}$ in brewer's yeast improved glucose tolerance, decr. peak insulin levels and decr. serum cholesterol	Offenbacher and Pi-Sunyer (1980)
5	diabetics	decrease in glucose clearance rate correlated with elevation of fasting urinary Cr (functional Cr deficiency)	Mertz (1979)
6	healthy adults supplied with 200 $\mu g.d^{-1}$ Cr^{3+} for 3 months	(i) 17 of 18 with marginally low glucose removal rate improved (ii) subjects with abnormally high glucose removal rate slowed to normal values	Anderson et al. (1983), Polansky et al. (1981)
7	hyperglycemic women	4 $\mu g\ Cr.d^{-1}$ as GTF for 3 mo. incr. $\Delta Cr\ U^{\beta}$ in 75%, reduced peak insulin level in 35% and reduced max. blood glucose in 75% of group	Liu and Morris (1978)

Table 5. (Cont'd)

	Subjects	Observations	Reference
8	alcoholic cirrhotics	impaired glucose tolerance ameliorated by 10 g brewer's yeast per day for 6 days	Rowden et al. (1977)
9	young adults with normal glucose tolerance but high insulin response to glucose	group had little if any change in serum Cr in response to glucose (as in compensated Cr deficiency)	Liu and Abernathy (1982)
10	hyperlipidemics	48 µg Cr in brewer's yeast per day for 8 wk decr. serum cholesterol from 269 to 246 $mg.dL^{-1}$ ($p \leq 0.05$)	Elwood et al. (1982)
11	relatives of diabetics having normal glucose tolerance	ΔCr U ≈0 indicative of Cr functional deficiency preceeding a diabetic state	Gurson and Saner (1978)
12	normal women	4 µg $Cr.d^{-1}$ as GTF for 3 mo increased ΔCr U in 73%, reduced peak insulin level in 23%, and reduced max. blood glucose in 73% of the group	Liu and Morris (1978)
13	healthy adults	Cr in brewer's yeast added to diet decr. serum cholesterol 18%	Doisy et al. (1976)
14	healthy men aged 31-60 y having normal glucose tolerance	200 µg $Cr^{3+}.d^{-1}$, 5 $d.wk^{-1}$ for 12 wk signif. incr. high density lipoprotein cholesterol in serum, effect most noticeable in those having elevated fasting insulin levels; total cholesterol remained unchanged	Riales and Albrink (1981)
15	normolipidemics	48 µg Cr in brewer's yeast per day for 8 wk decr. serum cholesterol from 205 to 179 $mg.d^{-1}$ ($p \leq 0.01$)	Elwood et al. (1982)

α Note: Vallerand et al. (1984) found, in contrast, that exercise increases Cr levels in rat heart, liver, kidney and muscle and largely prevents the decline of Cr levels which normally occurs with increasing age. Increased intake of food and drink may more than compensate for increased Cr excretion after strenuous exercise.

β ΔCr U = urinary Cr concentration change in response to a glucose challenge.

Table 6. Recent developments in analysis of Cr in biological and environmental samples.

Sample type	Method	Reference
airborne particulate	electron microscopic particle sizing PIXE[α] for total Cr ESCA[β] for Cr speciation chelation - extraction for 'soluble' Cr	Bohgard et al. (1979)
sea water	$Fe(OH)_3$ co-precipitation - flameless AA[γ] speciation of CrIII, CrVI, complexed Cr	Nakayama et al. (1981)
"	total Cr; diphenylcarbazone pre-concentration; electrothermal atomic absorption with Zeeman background correction	Willie et al. (1983)
"	complexation, isotope dilution, GC-MS[δ]	Siu et al. (1983)
"	CrIII - luminol chemiluminescence	Chang et al. (1980)
"	CrVI extraction with APDC[ε]; isotope-dilution mass spectrometry	Osaki et al. (1976)
fresh water	filtration, co-precipitation with $Fe(OH)_3$, flameless AA	Cranston and Murray (1980)
"	CrIII/CrVI speciation using HPLC[ζ]-DC plasma emissions spectrometry	
plant tissue	chemical separation, electrothermal AA no background correction needed	Cary and Rutzke (1983)

Table 6. (Cont'd)

Sample type	Method	Reference
biological tissue	paramagnetic CrIII or CrVI by ESR[η]	Gutierrez et al. (1976); Baquey (1976)
blood plasma	flameless AA using 358.5 nm uranium line for background correction	Thompson (1980)
urine	electrothermal AA, necessity for background correction	Guthrie et al. (1978)
"	direct electrothermal AA	Ping et al. (1983)
"	standard method using electrothermal AA and background correction	Veillon et al. (1982)
biological material	biologically active (GTF) Cr determined using rat fat-cell assay	Anderson et al. (1978)

[α] PIXE = proton-induced X-ray emission.

[β] ESCA = electron spectroscopy for chemical analysis.

[γ] AA = atomic absorption.

[δ] GC-MS = gas chromatography mass spectrometry.

[ε] APDC = ammonium pyrrolidine dithiocarbamate.

[ζ] HPLC = high performance liquid chromatography.

[η] ESR = electron spin resonance.

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